

DMB

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Display Date	8/28
Publication Date	8/29
Certifier	<i>[Signature]</i>

21 CFR Part 333

[Docket No. 99N-1819]

RIN 0910-AA01

Topical Antifungal Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the monograph for over-the-counter (OTC) topical antifungal drug products. The amendment makes a minor change in the indications for these drug products. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

DATES: This regulation is effective May 16, 2002. The compliance date for products with annual sales less than \$25,000 is May 16, 2003. The compliance date for all other OTC drug products is May 16, 2002.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2307.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 23, 1993 (58 FR 49890), FDA published a final monograph for OTC topical antifungal drug products in part 333 (21 CFR part 333), subpart C.

NER 1

That monograph includes labeling in § 333.250. Section 333.250(b)(1) contains the following introductory language for the indications statement: (Select one of the following: “Treats,” “For the treatment of,” “For effective treatment of,” “Cures,” “For the cure of,” “Clears up,” or “Proven clinically effective in the treatment of”). Section 333.250(b)(2) contains similar language for products labeled for the prevention of athlete’s foot.

In the **Federal Register** of July 22, 1999 (64 FR 39452), FDA published a proposed amendment of the monograph for OTC topical antifungal drug products to revise the indications in § 333.250(b)(1)(i) and (b)(2)(i). The proposed revision added the word “most” after the introductory parenthetical “Select one of the following” choices and before the name of the condition(s) for which the product is to be used. The agency also proposed to add the word “most” in § 333.250(b)(2)(ii) after the word “up” and before “athlete’s foot.” The agency explained that topical antifungal drug products will not cure or treat all conditions commonly thought by consumers to be athlete’s foot or jock itch and that the revised labeling will more accurately inform consumers what they can expect from using these products. The agency stated that this approach is consistent with the current labeling approved for OTC vaginal antifungal drug products under new drug applications, which states “cures most vaginal yeast infections.”

Interested persons were invited to submit comments on the proposal and on the agency’s economic impact determination by October 20, 1999. In response to the proposed monograph amendment, one trade association of OTC drug manufacturers submitted a comment, a copy of which is on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville. MD 20852.

The agency has considered the comment in proceeding with this final rule. A summary of the comment with FDA’s response follows.

II. Summary of the Comment Received

The comment requested FDA to decide against the proposed amendment for several reasons:

1. Scientific documentation is lacking to show that adding the qualifier “most” would meet an important consumer need or is important for safe and effective use of these products. The comment noted that in the tentative final monograph for OTC topical antifungal drug products (54 FR 51136 at 51154, December 12, 1989) the agency stated that the statement “kills most athlete’s foot fungi” described the performance of the product and was not related in a significant way to the safe and effective use of antifungal drug products that are already labeled with the required information. The comment contended that FDA did not provide information showing that addition of the word “most” relates in a significant way to the safe and effective use of OTC topical antifungal drug products or would have any value in assisting consumers to better use these products.

2. The use of a qualified indication statement resulting from addition of the word “most” is unprecedented in the OTC drug review. The comment noted that no other OTC drug monograph requires a statement that qualifies the effect of a drug category and questioned why topical antifungal drug products are now an exception to this labeling policy that has consistently omitted effectiveness qualifiers.

3. A qualified indications statement is potentially misleading, in that it implies inherent lack of efficacy of the active ingredient or questionable effectiveness of the drug product. The comment contended that this approach is inconsistent with the regulatory definition of effectiveness for OTC drug monograph products in § 330.10(a)(4)(ii) (21 CFR 330.10(a)(4)(ii)), which states:

“Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed.”

The comment argued that the standard for effectiveness does not require that every user of an OTC topical antifungal drug product gets complete relief (or prevention) for the condition for which he or she chose the product. The comment added that the monograph already requires a warning

statement to consult a doctor if the product is not effective within the recommended treatment period.

4. Differences in labeling would occur between OTC drug products marketed under the monograph versus marketed under an approved application, resulting in consumer confusion. The comment noted that the amendment applies only to the monograph products and that FDA should coordinate label changes for all OTC products within a therapeutic category. The comment added that if monograph product labels are inconsistent with new drug application product labels for the same category of products, consumers could mistakenly believe that the monograph products are less effective because they are labeled to treat only “most” covered conditions.

III. The Agency’s Response to the Comment and Final Conclusions

The agency disagrees with the comment’s request to decide against the proposed amendment and is responding to the comment’s reasons in the order in which they appear in section II of this document.

1. As stated in the proposed amendment (64 FR 39452), the agency believes that addition of the qualifier “most” to the indications for OTC antifungal drug products would more accurately inform consumers what they can expect from using these products. When it proposed this labeling revision, the agency was aware of previous labeling claims it had discussed in the tentative final monograph (54 FR 51136 at 51154), as noted by the comment. The agency stated, at that time, that the claim “kills most athlete’s foot fungi” was one of a number of claims that did not relate in a significant way to the safe and effective use of antifungal drug products that are labeled with the required information.

The agency notes that the Advisory Review Panel on OTC Antimicrobial (II) Drug Products (the Panel) discussed this claim in its report (47 FR 12480 at 12511, March 23, 1982). The Panel stated that “Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as ‘most’ or ‘fast’ are not allowed.” The Panel then listed the claim “kills most athlete’s foot fungi” as unacceptable.

As noted in the proposed amendment (64 FR 39452), the word “most” is currently used in the labeling of OTC vaginal antifungal drug products, which are marketed under new drug applications. This labeling has been in effect since late 1990 when these products were initially approved for OTC marketing. In making its decision to include the word “most” in the labeling of these products, the agency disagreed with the Panel and its previous position stated in the tentative final monograph for OTC antifungal drug products. The agency now considers it imprecise not to state in the labeling of all OTC antifungal drug products that they treat or cure or prevent “most” athlete’s foot [and the other treatment claims listed in the monograph]. As discussed in the proposal (64 FR 39452), topical antifungal drug products will not cure or treat all conditions commonly thought by consumers to be athlete’s foot or jock itch. In addition, data reviewed by the Panel for the various monograph ingredients showed that varying percentages of subjects were clinically and mycologically “cured.” The agency, therefore, concludes that inclusion of the word “most” in the labeling of these products is related to their effective use and will assist consumers in knowing better what to expect from using these products.

2. The agency disagrees with the comment’s assertion that it is the agency’s policy to omit effectiveness qualifiers. In addition, the use of a qualified indication statement resulting from addition of the word “most” is not unprecedented in the OTC drug review. The final monograph for OTC topical acne drug products contains the following indication statement in § 333.350(b)(2)(ii): “Penetrates pores to” (select one of the following: “eliminate most,” “control,” “clear most,” or “reduce the number of”) (select one or more of the following: “acne blemishes,” “acne pimples,” “blackheads,” or “whiteheads”). The agency notes that both acne and antifungal drug products are included in the same part 333 of the *Code of Federal Regulations*, entitled “topical antimicrobial drug products for over-the-counter human use.” As discussed above, the agency concludes that the qualifier “most” will assist consumers in knowing better what to expect from using these products.

3. The agency disagrees that a qualified indications statement is potentially misleading or that it implies inherent lack of efficacy of the active ingredient or questionable effectiveness of the drug product. The regulatory definition of effectiveness in § 330.10(a)(4)(ii) (see section II.3 of this document) provides sufficient latitude for the word “most” in describing the pharmacological effect of the drug and relief of the type claimed. Many indications in OTC drug monographs contain qualifiers of one kind or another, e.g., “helps,” “reduces,” “occasional,” “temporarily,” “temporary relief.” Even with this qualifier in the indications statement, these OTC drug products also contain a warning statement to consult a doctor if relief is not obtained, just as the topical antifungal drug products do. The agency concludes that the presence of such a warning statement in the product’s labeling is not a sufficient basis not to have a qualified indications statement.

4. The agency does not intend for labeling differences to occur between topical antifungal drug products marketed under the monograph or an approved application. While the amendment applies only to the monograph products, the agency intends to notify all holders of approved new drug applications for OTC topical antifungal drug products to revise their product labeling in accord with the monograph by the effective date of the amendment. Thus, the labeling changes will have a coordinated effective date, and consumer confusion should not occur.

In conclusion, the agency is finalizing its proposal to amend the monograph indications statements by inserting the word “most” between the introductory phrase and the name of the condition(s) for which the OTC topical antifungal drug product is to be used. Accordingly, the agency is revising the indications in § 333.250(b)(1)(i) and (b)(2)(i) to add the word “most” after the introductory parenthetical “Select one of the following” choices and in § 333.250(b)(2)(ii) to add the word “most” after the word “up.” This “treats most” or “cures most” language must also be used whenever the alternative labeling approach allowed by § 330.1(c)(2) (21 CFR 330.1(c)(2)) is used or whenever a general statement containing this information appears in the labeling of the product (e.g., on the principal display panel).

IV. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501*et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The purpose of this final rule is to make a minor revision in the indications for OTC topical antifungal drug products. This revision should improve consumers' self use of these products by better informing them about what they can expect from using the products.

The agency stated in the proposal that manufacturers of these products will incur minor costs to relabel their products to revise the indications statement and, in some cases, other statements that appear in product labeling (64 FR 39452 at 39453). The agency indicated that relabeling costs of the type required by this rule generally average about \$2,000 to \$3,000 per stockkeeping unit (SKU) (individual products, packages, and sizes). In determining this cost, the agency did not believe that manufacturers would need to increase the package size to make this minor labeling

revision. Almost all of these products are marketed in an outer carton which should have adequate space for the minor labeling revision. The agency noted that approximately 50 manufacturers produce about 200 SKU's of OTC topical antifungal drug products marketed under the monograph. There may be a few additional small manufacturers or products in the marketplace that are not identified in the sources FDA reviewed. Assuming that there are about 200 affected OTC SKU's in the marketplace, FDA estimated that the rule would impose total one-time compliance costs on industry for relabeling of about \$400,000 to \$600,000. The agency did not receive any comments on these estimates.

The agency believes the actual cost could be lower for several reasons. First, most of the label changes will be made by private label small manufacturers that tend to use simpler and less expensive labeling. However, the final rule will not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. Second, the agency has made the compliance dates for this final rule the same as the dates for these monographed products to be in compliance with the new standardized format and standardized content requirements for the labeling of OTC drug products (21 CFR 201.66), which are now May 16, 2002 (and May 16, 2003, for products with annual sales less than \$25,000). Thus, all required labeling changes can be made at the same time, thereby reducing the labeling cost of this final rule.

The agency considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, the agency also acknowledges that coordination of this labeling change with implementation of the new OTC "Drug Facts" labeling may significantly reduce the cost of this final rule. Both a shorter and a longer time period for this rule may cost more if firms would have to undertake two successive labeling revisions. In addition, a longer time period would unnecessarily delay the benefit of the new labeling to consumers who self-medicate with these OTC antifungal drug

products. The agency rejected an exemption for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities.

Under the Unfunded Mandates Reform Act, FDA is not required to prepare a statement of costs and benefits for this final rule because this final rule is not expected to result in any one-year expenditure that would exceed \$100 million adjusted for inflation.

This analysis shows that the agency has considered the burden to small entities. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this final rule are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the indications statements are a "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 333

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 333 is amended as follows:

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 333 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 333.250 is amended by revising paragraphs (b)(1)(i), (b)(2)(i), and (b)(2)(ii) to read as follows:

§ 333.250 Labeling of antifungal drug products.

* * * *

(b) * * *

(1) * * * (i) (Select one of the following: “Treats,” “For the treatment of,” “For effective treatment of,” “Cures,” “For the cure of,” “Clears up,” or “Proven clinically effective in the treatment of”) “most” (select one condition from any one or more of the following groups of conditions:

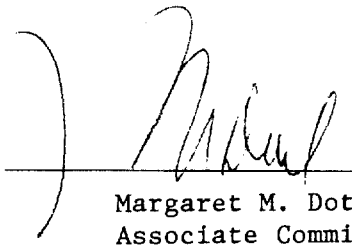
* * * *

(2) * * * (i) (Select one of the following: “Clinically proven to prevent,” “Prevents,” “Proven effective in the prevention of,” “Helps prevent,” “For the prevention of,” “For the prophylaxis (prevention) of,” “Guards against,” or “Prevents the recurrence of”) “most” (select one of the following: “Athlete’s foot,” “athlete’s foot (dermatophytosis),” “athlete’s foot (tinea pedis),” or “tinea pedis (athlete’s foot)”) “with daily use.”

(ii) In addition to the information identified in paragraph (b)(2)(i) of this section, the labeling of the product may contain the following statement: "Clears up most athlete's foot infection and with daily use helps keep it from coming back."

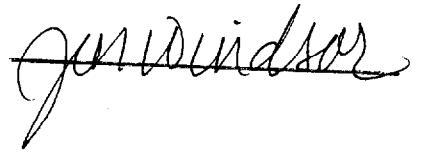
* * * * *

Dated: 8/15/00
August 15, 2000



Margaret M. Dotzel,
Associate Commissioner for Policy.

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL



Jennifer Windsor

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

BILLING CODE 4160-01-F